Hygiene factors associated with childhood food allergy and asthma

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ABSTRACT

Background: *Childhood food allergy and asthma rates are increasing. The hygiene hypothesis has been proposed as an explanation for the increased incidence of allergic disease.*

Objective: *To describe the association of childhood food allergy and asthma with hygiene factors, such as the number of siblings, antibiotic use, infection history, pet exposure, child care exposure, and maternal–child factors.*

Methods: *Children ages 0–21 years old (N = 1359) were recruited for a cross-sectional family-based study, including children with food allergy and children without food allergy, and their siblings. We assessed the associations between childhood food allergy and asthma with hygiene factors.*

Results: *Of the 1359 children, 832 (61.2%) had food allergy, and 406 (30%) had asthma. In the adjusted analysis, the prevalence of food allergy was increased if there was a history of skin infection (prevalence ratio [RRR] 1.12 [95% confidence interval {CI}, 1.01–1.24]) or eczema (RRR 1.89 [95% CI, 1.70–2.10]). The prevalence of asthma was increased with a history of respiratory syncytial virus infection (RRR 1.60 [95% CI, 1.34–1.90]) or eczema (RRR 1.54 [95% CI, 1.27–1.86]). A greater number of siblings were associated with a decreased prevalence of food allergy (RRR 0.79 [95% CI, 0.75–0.84]) and asthma (RRR 0.82 [95% CI, 0.74–0.91]).*

Conclusion: *Our findings supported the accumulating evidence of an association between skin infections and eczema with food allergy. Because these results could be subject to recall bias, additional prospective studies are needed to substantiate these findings.*

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One of every 13 children in the United States, nearly 6 million, has a food allergy,[1] and the incidence is increasing.[2] Although research has not yet elucidated the exact mechanism(s) responsible for the increase in childhood food allergy, the "hygiene hypothesis" has been proposed to explain the increasing incidence. The hygiene hypothesis was first described by Strachan[3] in 1989 to explain the rising incidence of asthma and proposes that early microbial exposure impacts the immune system, which thus decreases the risk for allergic disease.[4] Although this hypothesis has been well studied for asthma, it has not yet been extensively studied for food allergy. Results of recent studies showed that early life viral infections, such as rhinovirus[5] and respiratory syncytial virus (RSV),[6,7] may be associated with increased asthma. With regard to food allergy, skin barrier deficiencies, *e.g.*, atopic dermatitis, have been associated with food allergy and food sensitization.[8,9]

Here, we used a sample of children with and without food allergy to assess whether hygiene factors are associated with a food allergy and/or asthma diagnosis. We investigated key hygiene factors, including, antibiotic use, infections, siblings, pets, maternal child health factors and child care, and their association with food allergy and asthma in the same cohort of patients in which many showed comorbidity. This design allowed us to explore the influences of these factors on asthma or food allergy in the same patients and families.

METHODS

Sample Recruitment

A total of 2834 children were enrolled in the Chicago Family Cohort Food Allergy study. The present study

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included 1359 of those children. Families with one or both parents, and at least one biologic child (ages 0–21 years) with food allergy were eligible to participate. Parents and other siblings were not required to have a food allergy to participate. Families were recruited through general pediatric and allergy specialty clinics, community support groups, and media advertisements. The institutional review board of the Ann and Robert H. Lurie Children's Hospital of Chicago approved the study protocol. All participating families provided written informed consent. For these analyses, we included all children within the recruited families. This included children who had food allergy and/or asthma and those who had neither.

Food Allergy Status

Food allergy status was determined by board-certified allergists (J.P.) by applying a set of clinical criteria to data gathered from a questionnaire, and results from specific immunoglobulin E and skin-prick testing. Clinical criteria for food allergy were met if positive test results (specific immunoglobulin E or skin test) corroborated typical symptoms of an allergic reaction to that food with onset within 2 hours of ingestion by parental report. A specific immunoglobulin E level of >0.35 kUA/L was considered positive, and a positive skin-prick test result was defined as a mean wheal diameter of ≥ 3 mm than the saline solution control. Symptoms were assessed for each reported allergen by an allergist (J.P.) and included any of the following: hives or angioedema (skin); difficulty breathing, shortness of breath, repetitive coughing, wheezing, or chest tightness (respiratory tract); throat tightness, choking, or difficulty swallowing; tongue swelling (oropharynx); fainting, dizziness, light-headedness, or decreased level of consciousness (cardiovascular system); or vomiting (gastrointestinal tract).

Outcome Measurements

Trained research staff (D.C.) administered a structured questionnaire to each parent about their child's history of food allergy, asthma, number of siblings, antibiotic use, infections, pets, maternal child health factors, and child care. For asthma and eczema, a physician diagnosis was required as well as the age of diagnosis. Asthma medications were also reported. For antibiotic use, the parents were asked about the number of times that their child took antibiotics in his or her first year of life. A brief description and examples of antibiotics were provided. For infections, the parents were asked about the number of times that their child had any of the following illnesses in the first year of life: common cold, gastric and/or intestinal infections, conjunctivitis, ear infections, pneumonia, skin infection, urinary tract infections, parasite infections, bone infections, meningitis, bacteremia and/or sepsis, and/or sinus infections.

For pet ownership, the parents were asked to report the number and type of pet that was present during the child's first year of life. These included the following: cat, dog, fish, bird, reptile, rabbit, guinea pig, and other. The parents were also asked questions about mode of delivery (caesarean section or vaginal), child care, and breast-feeding practices. Child care questions included whether the child was cared for outside of the home before age 5 years: where (*i.e.,* child care center or preschool, home-based child care in someone else's home, home-based child care in the parents' own home), duration, and the number of other children present in the child care setting. For breast-feeding, the mothers were asked if the child was breast-fed, bottle fed, or both, how long they exclusively breast-fed, and how long they breast-fed both with and without formula supplementation.

Statistical Analysis

To characterize the association between hygiene factors, food allergy, and asthma, the prevalence of current food allergy and asthma were calculated overall and for subgroups of the participants. The unadjusted association between risk factors and the outcome measures were examined by using χ^2 tests for categorical variables and the difference of means tests for risk factors that were continuous. We also estimated Poisson regression models for each risk factor. To explore the adjusted association between risk factors and outcomes, and to estimate prevalence ratios, separate Poisson regression models that included standard errors that were adjusted for clustering within families, were estimated.[10] All statistical analyses were completed by using STATA statistical software (StataCorp LP, College Station, TX).

RESULTS

Demographic Characteristics

Demographic characteristics are shown in Table 1. All the participants in the study completed the baseline questionnaire; a total of 984 families were included in these analyses. Forty-three percent of the subjects were children ages 2–5 years old, with an average of two siblings per household (49.3%). The participants were predominantly non-Hispanic white (74.5%). Thirty percent of the children in the study had asthma (5.3% had asthma only), 61.2% had a food allergy (36.6% had food allergy only), 33.4% had neither, and 24.6% had both food allergy and asthma.

Infections and Antibiotic Use

In the unadjusted analysis, food allergy was significantly increased if a parent reported that a child had a

Table 1 **Demographic characteristics**

Variables	Frequency, % (no.)				
	Children with Food Allergy (832)	Children without Food Allergy (527)	Children with Asthma (406)	Children without Asthma (953)	All Children (1359)
Age					
0–1 y	12.4 (103)	19.4 (102)	3.5 (14)	20.0 (191)	15.1 (205)
2–5 y	48.2 (401)	34.9 (184)	42.1 (171)	43.4 (414)	43.1 (585)
6–10 y	28.1 (234)	31.1 (164)	36.0 (146)	26.4 (252)	29.3 (398)
11–13 y	6.9 (57)	8.2 (43)	10.8 (44)	5.9 (56)	7.4 (100)
14–20 y	4.5 (37)	6.5 (34)*	7.6 (31)	4.2 (40)*	5.2 (71)
Sex					
Boys	61.7 (513)	47.8 (252)	66.5 (270)	51.9 (495)	56.3 (765)
Girls	38.5 (319)	52.2 (275)*	33.5 (136)	48.1 (458)*	43.7 (594)
Race or ethnicity					
White	75.8 (631)	72.3 (381)	75.1 (305)	74.2 (707)	74.5 (1012)
Black	4.5 (37)	6.6 (35)	7.1 (29)	4.5 (43)	5.3 (72)
Hispanic	9.3 (77)	12.1 (64)	9.9 (40)	10.6 (101)	10.4 (141)
Asian	2.8 (23)	2.3 (12)	2.5 (10)	2.6 (25)	2.6 (35)
Other	7.7 (64)	6.6 (35)	5.4 (22)	8.1 (77)	7.3 (99)
Other atopy					
Food allergy	—	—	82.3 (334)	52.3 (498)*	61.2 (832)
Asthma	61.5 (513)	47.8 (252)*	—	—	29.9 (406)
Eczema	51.8 (432)	23.0 (121)*	48.5 (197)	37.3 (355)*	40.6 (552)
Hay fever	50.7 (422)	22.6 (119)*	67.2 (273)	28.2 (268)*	39.8 (541)
Other allergies	66.0 (549)	20.7 (109)*	78.1 (317)	35.8 (341)*	48.4 (658)
Family structure					
Single parent	4.9 (41)	11.4 (60)	9.6 (39)	6.5 (62)	7.4 (101)
Married parents	95.1 (791)	88.6 (467)*	90.4 (367)*	93.5 (891)*	92.6 (1258)
Sibling status					
0	22.5 (187)	5.7 (30)	16.0 (65)	16.0 (152)	16.0 (217)
1	51.6 (429)	45.7 (241)	56.2 (228)	46.4 (442)	49.3 (670)
2	20.9 (174)	35.7 (188)	23.7 (96)	27.9 (266)	26.6 (362)
≥3	5.0 (42)	12.9 (68)*	4.2 (17)	9.8 (93)*	8.1 (110)
Family history of food allergy					
Mother affected	20.1 (167)	14.6 (77)*	20.9 (85)	16.7 (159)	18.0 (244)
Father affected	18.2 (151)	16.1 (85)	18.7 (76)	16.8 (160)	17.4 (236)
Both parents affected	3.2 (27)	1.9 (10)	3.0 (12)	2.6 (25)	2.7 (37)
Family history of any atopy					
Mother affected	80.2 (667)	78.0 (411)	82.0 (333)	78.2 (745)	79.3 (1078)
Father affected	71.0 (591)	66.4 (350)	75.1 (305)	66.7 (636)*	69.2 (941)
Both parents affected	57.6 (479)	52.4 (276)	61.8 (251)	52.9 (504)*	55.6 (755)
Household income					
<$50,000	7.7 (64)	16.1 (85)	12.6 (51)	10.3 (98)	11.0 (149)
$50,000–$100,000	27.9 (232)	31.1 (164)	29.3 (119)	29.1 (277)	29.1 (396)
>$100,000	61.4 (511)	50.5 (266)	54.4 (221)	58.3 (556)	57.2 (777)
Missing	3.0 (25)	2.3 (12)*	3.7 (15)	2.3 (22)	3.0 (37)
Housing structure					
Condo or apartment	10.5 (87)	12.7 (67)	11.3 (46)	11.3 (108)	11.3 (154)
Others	89.5 (745)	87.3 (460)	88.7 (360)	88.7 (845)	88.7 (1205)

*$p < 0.01$.

Table 2 **Maternal child health associations and out-of-home child care**

Proxy Measures	Frequency, % (no.)			
	Children with Food Allergy	Children without Food Allergy	Children with Asthma	Children without asthma
Out-of-home child care before age 5 (*i.e.,* child care center or preschool)				
Yes, any out-of-home child care	76.6 (621)	70.4 (371)	82.0 (33)	69.2 (659)
Child care center or preschool	67.2 (559)	66.2 (349)	76.4 (310)	62.8 (598)**
Home-based child care	21.3 (177)	19.7 (104)	24.4 (99)	19.1 (182)*
MCH associations				
Maternal age				
Maternal age at birth, mean ± SD	32.2 ± 4.2	30.9 ± 4.7	31.7 ± 4.7	31.7 ± 4.4
Caesarean-section birth, yes	28.9 (240)	29.2 (154)	32.3 (131)	27.6 (263)
Breast-feeding				
Exclusive breast-feeding	21.9 (182)	23.2 (122)	20.2 (82)	23.3 (222)
Duration, mean ± SD	5.7 ± 3.7	5.3 ± 3.4	6.1 ± 4.9	5.4 ± 3.0
Any breast-feeding	92.0 (765)	88.8 (468)	90.2 (366)	91.0 (867)
Duration, mean ± SD	10.4 ± 7.3	10.3 ± 8.3	10.2 ± 7.2	10.4 ± 7.9

MCH = Maternal Child Health; SD = standard deviation.
*$p < 0.05$; **$p < 0.01$.*

skin infection (7.9 versus 2.1%; $p < 0.01$), common cold (79.6 versus 73.8%; $p < 0.05$), or pneumonia (3.9 versus 1.7%; $p < 0.05$). Antibiotic use showed no significant association with food allergy. Asthma was increased if a child had a previous infection, including common cold (81.5 versus 45.6%; $p < 0.05$), RSV (21.4 versus 8.6%; $p < 0.01$), pneumonia (5.4 versus 2.0%; $p < 0.01$), ear infection (45.6 versus 39.1%; $p < 0.05$), or skin infection (7.9 versus 4.7%; $p < 0.05$). Similarly, antibiotic use significantly increased the child's chances for current asthma (59.9 versus 51.5%; $p < 0.01$). We also tested the models for multicollinearity by calculating the variable inflation factors for the independent covariates. The mean variable inflation factor was 1.11; often values of >10 are considered collinear, but, even if we used a more conservative cutoff of 2.5, our highest variable inflation factor value for any variable was 1.33.

Maternal Child Health Factors and Child care

For children with food allergy, no significant associations with maternal child health factors (maternal age, caesarean section, breast-feeding, or out-of-home child care) were found. In contrast, out-of-home child care in a center or preschool (76.4 versus 62.8%; $p < 0.01$) and home-based child care (24.4 versus 19.1%; $p < 0.05$) were each significantly associated with current asthma (Table 2 and Table E1 [Supplemental data available at www.IngentaConnect.com]).

Pet Exposure

In the unadjusted analysis, for children with food allergy, no significant associations with pet ownership were found. However, for children with asthma, cat ownership showed a significant inverse association (10.3 versus 18.3%; $p < 0.01$).

Adjusted Analyses

The following variables were controlled for in the adjusted analysis based on previous studies, parent-reported infections, eczema, antibiotic use, age, race, sex, household income, pets, parental atopy, number of siblings, breast-feeding, and child care. A parent-reported history of skin infection (prevalence ratio [RRR] 1.12 [95% confidence interval {CI}, 1.01–1.24]) and eczema (RRR 1.89 [95% CI, 1.70–2.10]) were associated with increased prevalence of food allergy, whereas the number of siblings (RRR 0.79 [95% CI, 0.75–0.84]) and child care in a child care center (RRR 0.92 [95% CI, 0.85–1.00]) were associated with decreased prevalence of food allergy. For asthma, parent-reported RSV (RRR 1.60 [95% CI, 1.34–1.90]), and eczema (RRR 1.54 [95% CI, 1.27–1.86]) were associated with increased prevalence, whereas the number of siblings (RRR 0.82 [95% CI, 0.74–0.91]), and owning a cat (RRR 0.64 [95% CI, 0.49–0.85]) were associated with decreased prevalence (Table 3).

DISCUSSION

In this study, we investigated the relationship among factors related to hygiene and food allergy and asthma,

Table 3 **Regression Model**

Variables	Food Allergy vs None, unadjusted RRR (95% CI)	Food Allergy vs None, adjusted RRR (95% CI)	Asthma vs None, unadjusted RRR (95% CI)	Asthma vs None, adjusted RRR (95% CI)
Hygiene factors				
Cold in first year	1.14 (1.02–1.28)*	1.09 (0.98–1.20)	1.29 (1.03–1.63)*	1.23 (0.99–1.54)
RSV in first year	1.10 (0.98–1.23)	0.98 (0.88–1.08)	1.92 (1.61–2.29)**	1.60 (1.34–1.90)**
Skin infection	1.43 (1.30–1.58)**	1.12 (1.01–1.24)*	1.42 (1.08–1.88)*	1.17 (0.89–1.52)
Eczema	2.12 (1.89–2.35)**	1.89 (1.70–2.10)**	1.82 (1.50–2.20)**	1.54 (1.27–1.86)**
Antibiotic use during first year	1.02 (0.94–1.11)	0.97 (0.89–1.05)	1.27 (1.07–1.50)**	1.02 (0.86–1.21)
Age				
2–5 y	1.36 (1.18–1.58)**	1.44 (1.25–1.65)**	4.28 (2.57–7.13)**	3.96 (2.36–6.65)**
6–10 y	1.17 (1.00–1.37)	1.34 (1.15–1.56)**	5.37 (3.19–9.03)**	5.41 (3.17–9.23)**
11–13 y	1.13 (0.91–1.42)	1.37 (1.12–1.67)**	6.44 (3.71–11.20)**	6.80 (3.86–11.98)**
14–20 y	1.04 (0.80–1.35)	1.24 (0.99–1.54)	6.39 (3.57–11.44)**	6.23 (3.44–11.28)**
White race	1.08 (0.97–1.20)	1.03 (0.94–1.13)	1.04 (0.85–1.27)	1.13 (0.95–1.36)
Male sex	1.25 (1.14–1.37)**	1.11 (1.02–1.21)*	1.54 (1.28–1.85)**	1.37 (1.15–1.63)**
Household Income				
$50,000–100,000	1.36 (1.11–1.68)**	1.31 (1.10–1.56)**	0.89 (0.68–1.17)	0.77 (0.59–1.01)
>$100,000	1.53 (1.25–1.87)**	1.41 (1.19–1.67)**	0.82 (0.64–1.06)	0.66 (0.51–0.84)**
Pets				
Dog	0.94 (0.86–1.04)	0.92 (0.85–1.00)	0.90 (0.74–1.11)	0.91 (0.75–1.10)
Cat	0.90 (0.79–1.02)	0.91 (0.82–1.01)	0.61 (0.46–0.81)**	0.64 (0.49–0.85)**
Family history				
Mother with any atopy	1.05 (0.95–1.17)	1.06 (0.97–1.15)	1.19 (0.94–1.50)	1.13 (0.91–1.40)
Father with any atopy	1.09 (0.99–1.20)	1.05 (0.97–1.13)	1.34 (1.09–1.65)**	1.26 (1.04–1.52)*
No. siblings	0.75 (0.71–0.80)**	0.79 (0.75–0.84)**	0.85 (0.77–0.94)**	0.82 (0.74–0.91)**
Maternal child health				
Breast-feeding only	0.97 (0.88–1.07)	1.09 (0.99–1.19)	0.88 (0.71–1.09)	0.96 (0.79–1.18)
Child care				
Home-based	1.04 (0.93–1.15)	0.95 (0.87–1.04)	1.24 (1.03–1.49)*	1.04 (0.87–1.25)
Child care center	1.02 (0.93–1.11)	0.92 (0.85–1.00)*	1.60 (1.31–1.96)**	1.17 (0.96–1.42)

RRR = Prevalence ratio; CI = confidence interval; RSV = respiratory syncytial virus.
#These models were adjusted for hygiene factors, age, race, sex, household income, pets, family history, breast-feeding history, and child care history.
$^{*}p < 0.05$; $^{**}p < 0.01$.

including antibiotic use, infections, the number of siblings, pets, maternal child health factors, and child care. Interestingly, factors associated with food allergy were different than factors associated with asthma. For food allergy, skin infection and eczema in the first year of life were associated with increased prevalence, whereas the number of siblings and child care in a child care center were associated with decreased prevalence. For asthma, RSV and eczema were associated with increased prevalence, whereas the number of siblings and owning a cat were associated with decreased prevalence.

Analysis of our data indicated that skin infections and eczema in the first year of life were independently associated with food allergy. This was of particular interest, given evidence of the skin as a sensitizing area of exposure in food allergy.[11] In addition, skin infections often occur in children with atopic dermatitis, and epicutaneous food exposure may be of increased consequence on skin with atopic dermatitis.[12] Skin barrier deficiency, either in the setting of epidermal mutations[8] or atopic dermatitis disease severity,[9] has been associated with food allergy and food sensitization. Skin infections may play a role in tissue-specific immune responses, which resulted in food sensitization through the skin. Common respiratory infections, such as the common cold, RSV, and pneumonia, were not significantly associated with food allergy after adjusted analysis, which indicated that respiratory infections may be less important in the development of food allergy compared with asthma.

For asthma, our data corroborated previous studies that showed an association with early life respiratory infections.[5–7] Infections of the lower respiratory tract with viruses, such as rhinovirus and RSV, have been well described as altering the development of the respiratory and/or immune system, which increases the likelihood of developing asthma, especially in children who are predisposed.[5,6,13,14] The responses in our study that related to RSV or respiratory infections were clearly associated with asthma but not with food allergy. Although previous studies showed associations between asthma and early lower respiratory tract viral infections, the literature that describes an association with early bacterial infections and antibiotic use with asthma is mixed.[15–19] In several studies of antibiotic use, infections and asthma have been inconclusive or circumstantial.[15,16] Our study indicated that there was no association between antibiotic use in the first year of life with the diagnosis of food allergy or asthma.

Children of larger families are often exposed to more infections from siblings than children of smaller families, which can lead to a decrease in atopic disease.[3,15] Analysis of our data provided supportive evidence to the finding that family size and allergic disease were inversely related. A similar increase in exposure to infection is seen in child care centers. Children who were cared for in a child care center had a decreased prevalence of food allergy in our sample, which has been indicated previously.[20] This inverse association supported the possibility that greater exposure to a diverse array of bacteria in early life can protect the child against atopic disease later in life.[3] Indeed, the microbiome may play a role in maintaining inflammatory homeostasis and immune regulation,[21] including in food allergy.[22]

The present study had several limitations. Our sample was composed of predominantly white, upper-income families. As such, our findings may not be generalizable to the U.S. population. Future studies should evaluate food allergy in more ethnically and socioeconomically diverse groups. Because information about the child's asthma, additional medical history, and hygiene factors were based solely on parents' report and not medical record review, recall bias existed, especially for questions that were asked about the child's infection history and antibiotic use in the first year of life. We also did not collect the specific month in which the child was given antibiotics. Regarding a food allergy diagnosis, although children were not food challenged, the definition of food allergy for this study was more stringent than most published large-scale epidemiologic studies of food allergy.[23–27] A unique strength of this study was that families of children with food allergy were enrolled along with their siblings, who may or may not had allergic diagnoses. The subjects and controls were of similar genetic makeup and were raised similarly. Thus, we were uniquely positioned to assess the role of different exposures on current food allergy and asthma.

CONCLUSION

Our study raised important questions regarding the contributions of hygiene factors in allergic diseases. Although our findings indicated influences of several of these factors on asthma, the associations with food allergy were less profound. The associations with eczema and skin infection to food allergy aligned more closely with the potential involvement of skin as a route of food allergy sensitization than the established influences of the hygiene hypothesis seen in asthma.

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